

The Evolution of Target Hemoglobin Levels in Anemia of Chronic Kidney Disease

Short title: Target hemoglobin levels in CKD

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Abstract:

Since the introduction of erythropoiesis-stimulating agents (ESAs) into clinical practice in 1989, considerable effort has been put forth towards identifying the optimal treatment strategy for managing anemia of chronic kidney disease (CKD). After initial treatment of only the most severely anemic patients, treatment was subsequently expanded to include most patients on dialysis and many non-dialysis CKD patients. Many nephrology societies and regulatory agencies have sought to identify the most appropriate hemoglobin levels to which ESA therapy should be targeted. As increasing evidence became available about the impacts of ESAs on varying endpoints including morbidity, mortality, and quality of life, the guidelines put forth by such agencies evolved over time. We will review the literature impacting these determinations through the past three decades and comment on how this informs the application of this knowledge to the care of patients today.

Clinical Summary:

- Target hemoglobin levels as recommended in guidelines by various organizations have evolved over time.
- Initial trends of increasing target hemoglobin levels were halted and partially reversed by trials revealing increased morbidity and mortality at higher targets.
- Due to limitations in the available data, it remains difficult to pinpoint a specific target range and within some boundaries clinician judgment about the appropriate target for a given patient remains paramount.

Introduction

Anemia is a frequent complication in patients with advanced CKD and affects a substantial majority of patients with ESKD. (1) Anemia is associated with decreased exercise tolerance, fatigue, and generally poorer quality of life. (2) The pathogenesis of anemia in CKD includes inadequate erythropoietin production. (3) Recombinant human erythropoietin (epoetin alfa) was first approved by the U.S. Food and Drug administration (FDA) in 1989 following a series of studies demonstrating safety, reduced need for blood transfusions, and improved quality of life (QoL) in patients on dialysis. (4-7) The approval of epoetin alfa was greeted with enthusiasm and saw its widespread application in management of patients with severe anemia. Therapy with epoetin alfa and later other erythropoiesis stimulating agents (ESAs) gradually broadened to less severely anemic patients. Over time, identification of the optimal hemoglobin (Hb) level for patients with ESKD and CKD has been a subject of considerable source of controversy. This review will explore the literature that informed guidelines and regulations over the three decades since epoetin alfa was first brought to market.

Initial Approval of Epoetin

Prior to the availability of recombinant human erythropoietin analogs, anemia was treated with frequent red blood cell transfusions. In the initial phase III study by Eschbach et al. of epoetin alfa, mean hematocrit (Hct) prior to treatment was 22.3%, corresponding to a Hb of 7.5 g/dL. (4) In the six months prior to study initiation, the 333 study patients received a total of 1030 RBC transfusions, at an average rate of 0.52 transfusions per patient per month. This initial study targeted a Hct of 35% +/- 3%. After 2 months of therapy, the average RBC transfusion

rate was <0.03 per patient per month and most often needed if blood was lost with surgery or dialysis. In early studies of QoL in patients treated with ESAs, improvements included energy and activity level, functional ability, sleep and eating behavior, disease symptoms, health status, satisfaction with health, sex life, well-being, psychological affect, life satisfaction, and happiness. (8)

The FDA approved epoetin alfa in June 1989 with a target Hct on the prescribing information of 30-33%. (9) In the label, it was advised that the maximum Hgb should be 36%, above which the medication should be held. Why the FDA chose this target range was a subject of dispute since higher Hct levels had been targeted in the pre-approval trials. (10) Reimbursement for EPO administration was withheld by the Health Care Finance Administration when Hct was above 36%.

In the ensuing years, studies were undertaken to understand the potential effects of higher Hct/Hb levels. In sum, various trials targeting higher Hb levels demonstrated: no increase in progression of CKD with a suggestion that treating to higher levels would delay progression of CKD; safety in PD; lack of benefit in regressing left ventricular hypertrophy (LVH); improvement in fatigue; and reduction in transfusions. (11-16)

Dialysis Outcomes Quality Initiative (DOQI)

The 1997 Dialysis Outcomes Quality Initiative (DOQI) recommendations for anemia management with erythropoietin analogs recommended a target Hct of 33-36. (16) The Anemia Work Group cited multiple lines of evidence for this higher target. For one, shorter survival in patients was observed with lower Hb 9.9 vs. 11.3. (17) Next, lower Hb is associated with LVH and the LVH was associated with a 2.9-fold increase in mortality rates. (18) Epoetin treatment was shown to induce partial regression of LVH. (19) Studies of QoL indicated negligible benefits in increasing from Hb of 8 up to 9-10, whereas benefits were observed with increases from 8 to 10 to 12 or higher. (20-22) Third, comparison of the achieved Hct of 35% in the phase III study and 30% in the phase IV study showed improved QoL at 35%. (4,23) In one cited study significantly improved health-related quality of life (HRQOL) scores among predialysis CKD patients across a variety of study instruments used by trained interviewers were observed in the treated group. (23) Fourth, exercise capacity improved in patients treated Hct >36% compared to those with Hct of approximately 30%. (25)

A few studies indicated potential downsides to higher target Hb including increased thrombosis and reduced dialysis clearance of certain solutes. (26) Preliminary results of the Normal Hematocrit Cardiovascular Trial (NHCT) also created a note for concern. (15) However, these negative signals were generally thought to be of questionable importance given the bulk of studies supporting higher Hct/Hb targets. (15) Enthusiasm for higher and hypothetically more physiologically normal Hb led to a series of randomized controlled trials searching for more definitive support of such targets.

Trials Before 2006

The first was the prospective, randomized, double-blind, open label NHCT by Besarab et al. (27) Published in 1998, the trial enrolled 1233 prevalent hemodialysis patients with CHF or ischemic heart disease. The principal objective was to compare time to event outcomes between patients treated with epoetin alfa to a 'normal' Hct of 42% +/- 3% vs. a lesser correction to 30% +/- 3%. The trial was discontinued at an interim analysis when the group treated to the Hct of 42% experienced more (202 events; 33%) of the primary endpoint of combined nonfatal MI and death compared to patients at Hct of 30 (164 events; 27%). The risk ratio for the primary endpoint in the "normal-hematocrit" group was 1.3, with 95% CI 0.9-1.9, indicating a nonsignificant but nonetheless concerning trend towards increased events. Due to this safety signal and the low probability of confirming the principal hypothesis, the study was stopped prior to its completion. In addition, there were higher rates of access thrombosis in the higher Hct arm: 243 patients (39%) vs. 176 patients (29%) in the low Hct arm ($p=0.001$). Benefits to higher hemoglobin were also observed. Overall mortality was less at higher Hct values. Physical function scores on quality of life assessments Medical Outcomes Study Short Form Health Survey (SF-36) were significantly improved in the higher Hct arm, although this has been disputed in a reanalysis of the data (28). Except for patients with known cardiac disease, the NHCT did not immediately lead to any change in guideline recommendations. However, it laid the groundwork for later studies that ultimately led to Hct/Hb lower targets.

Investigators from Canada and Europe conducted a double blind RCT in 596 incident hemodialysis patients comparing lower (9.5-11.5 g/dL) and higher (13.5-14.5) Hb targets. (14,15) This study's principal hypothesis was that higher Hb would result in a lower incidence of LVH as assessed by left ventricular volume index. Achieved Hb levels were 13.3 and 10.9 in the higher and lower target groups, respectively. There was no significant difference in LVH between the two groups ($P=0.87$). Mortality was similar, with 13 and 20 deaths in the higher and lower target groups, respectively.

Effects of normalization of Hb was examined in a Scandinavian trial of 416 pre-dialysis, hemodialysis and peritoneal dialysis patients. (29) This prospective, open-label, randomized trial compared subnormal hemoglobin (9-12 g/dL) to normal hemoglobin (13.5-15 g/dL in females and 14.5-16 g/dL in males). The study's aim was to compare mortality, adverse events, and QoL in CKD patients. Enrollment began in 1995. Protocol changes were undertaken to exclude patients with significant cardiovascular comorbidity after preliminary results of the NHCT became available in 1996. This contributed to a high withdrawal rate and limited final conclusions. Overall mortality was very similar with 29 deaths (13.4%) in the normal Hb arm and 27 deaths (13.5%) in the subnormal Hb arm. Additional results from this and other large trials are presented in Table 1.

The 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines initially recommended a target Hb of >11 g/dL, but not necessarily higher than 13 g/dL. (30) These guidelines were motivated by reports indicating higher QoL and observational associations of

decreased mortality at higher Hb levels. (10) Subsequent trial reports would lead to a revision of the KDOQI Hb target to 11-12 g/dL the following year.

CHOIR, CREATE, TREAT and Subsequent Analyses

The open-label Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) RCT published in November 2006 compared outcomes in 1432 nondialysis CKD (CKD 3-4; eGFR 15-50) patients in terms of a composite primary endpoint of death, MI, and hospitalization for heart failure. (31) Singh et al. assigned 715 subjects to a target Hb of 13.5 g/dl and 717 subjects to 11.3 g/dL. There were 125 events in the high Hb group compared to 97 events in the low Hb group (hazard ratio [HR] 1.34; 95% CI: 1.03 to 1.74, P=0.03). Similar to the NHCT, this study was stopped at an interim analysis because of the safety issues and very low probability of showing a positive result with continuation. Hospitalization occurred more often with high Hb, 369 (51.6%) vs. 334 (46.6%) of patients (P=0.03). Serious adverse events occurred more often with high Hb (P=0.02) and were most pronounced for congestive heart failure (P=0.02). The authors concluded the abstract, "The use of a target hemoglobin level of 13.5 g per deciliter (as compared with 11.3 g per deciliter) was associated with an increased risk and no incremental improvement in the quality of life."

Cardiovascular Risk Reduction by Early Anemia Treatment (CREATE) open-label RCT was published at the same time as CHOIR. Drüeke et al. randomized 603 European nondialysis CKD (eGFR 15-35) patients to Hb 13-15g/dL (group 1) vs. Hb 10.5-11.5 g/dL (group 2) utilizing epoetin beta. (32) The primary endpoint was time to first of eight cardiovascular events. The

lower Hb group experienced a slightly lower rate of cardiovascular events, but it was nonsignificant (47 vs. 58 events, HR 0.78, 95% CI 0.53-1.14, P=0.20). The authors concluded, “In patients with chronic kidney disease, early complete correction of anemia does not reduce the risk of cardiovascular events.”

A metanalysis of 9 trials and 5143 patients including data from CHOIR and CREATE was published in the Lancet in 2007. (34) Phrommintikul et al. identified a higher risk of overall mortality in patients treated to higher Hb targets (risk ratio 1.17, 95% CI 1.01–1.35; p=0.031). In the same analysis, a higher risk of access thrombosis was seen (1.34, 95% CI 1.16–1.54; p=0.0001) in patients treated to higher target Hb.

Subsequent to the publication of these studies, the FDA placed a new black box warning on the epoetin alfa prescribing information in 2007. (35) The warning highlighted the increased risk of death and serious cardiovascular events when epoetin alfa was administered to a Hb greater than 12/g/dL. (36) The prescribing information also deleted all QoL claims of epoetin treatment. Shortly thereafter, the KDOQI guidelines were amended to reflect a revised target Hb range of 11-12 g/dL. (37)

The largest and most recent RCT, the double-blinded, placebo-controlled Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), was published in 2009. (38) Pfeffer et al. studied 4038 patients with diabetes, nondialysis CKD (eGFR 20-60) and anemia. A total of 2012 patients were randomized to darbepoetin to a target Hb of >13 while the comparison placebo

arm of 2026 patients was only treated with “rescue” darbepoetin if Hb fell to <9 g/dL. There was a nonsignificant trend toward an increased rate of the primary endpoint (composite of death, nonfatal MI, congestive heart failure, stroke or hospitalization for myocardial ischemia) among subjects in the higher target Hb group (632 vs. 630 events, HR 1.05, 95% CI 0.93-1.17, P=0.41). Attention was focused on a higher rate of stroke observed in the high target Hb group (101 vs. 53 events, HR 1.92, 95% CI 1.38-2.68, P <0.001).

Response to Accumulated Evidence

In early 2010, representatives from the FDA expressed concerns in an editorial about adverse events occurring in the course of therapy with ESAs. (39) Several potential hypotheses for the mechanism of harm were expressed. First, the notion that high Hb levels directly increase cardiovascular risk is possible. Arguing against this are suggestions from multiple studies in which high Hb levels were associated with less cardiovascular risk; though this itself may be confounded by healthier patients having higher Hb levels. Next, a particular concern to the FDA was the possibility that rapid changes in Hb, oscillations in level, and overshoots may be playing a role, supported by some internal FDA analyses. Due to these concerns, a more conservative dose escalation regimen was implemented in TREAT. Despite this conservative dose escalation, a higher risk of stroke was nonetheless observed in the high target Hb arm. Third, off target trophic effects on vascular cells and tumor growth could account for some of the risk. The editorial also observed that “the overall quality-of-life effects [in NHCT, CHOIR, and TREAT] were small and inconsistent.”

Systematic reviews and meta-analyses published in 2010 sought to clarify the evidence to date coinciding with the recent publication of TREAT. QoL was examined in paired reviews published in AJKD. Johansen and colleagues reviewed the evidence in CKD patients on dialysis. (40) Analysis was complicated because many studies reviewed lacked controls and a variety of different instruments were used to assess certain physical domains affecting QoL. The review found some reasonable evidence to support the notion that treatment with ESAs compared to placebo enhanced both VO_{2PEAK} and physical functioning. However, they did not identify a conclusive benefit in treating moderate anemia (Hgb 10-12 g/dL) to levels above 12 g/dL.

Gandra et al. performed a systematic analysis of QoL in nondialysis CKD patients. (41) Eight of eleven studies reported a statistically significant improvement in energy. Gandra et al. also reported that 10 of 14 studies reported statistically significant improvements in physical function. Ultimately, these authors found a modest benefit to treating patients with untreated anemia (Hb <10 g/dL). However, the benefit of treating to higher targets (>13 g/dL) in terms of QoL could not be established.

The accompanying editorial to both reviews noted the deficit of appropriately blinded placebo controlled RCTs in the literature on QoL. (42) The lack of placebo predisposes to potential bias from the benefit of being in a study. The lack of blinding could prejudice patients to an expectation of benefit. Overall, there was little evidence to support a Hb target of higher than 12 g/dL. The available data lacked granularity to compare QoL with Hb increase from 10-11 g/dL to 11-12 g/dL, for example.

With respect to hard endpoints, a metanalysis published in May 2010 in *Annals of Internal Medicine* added TREAT data to pre-existing literature. (43) Utilizing data from 27 trials and 10,452 patients, Palmer and colleagues found that higher vs. lower Hb treatment targets resulted in higher risk of stroke (relative risk [RR] 1.51; 95% CI 1.03-2.21), vascular access thrombosis (RR 1.33; 95% CI 1.16-1.53) and hypertension (RR 1.67; 95% CI 1.31 to 2.12)). In contrast to the earlier metanalysis by Phrommintikul et al., with TREAT data included there was a nonsignificant trend toward increased mortality with higher Hb target (RR 1.09, 95% CI 0.99-1.20). Similarly, there were nonsignificant trends toward increased cardiovascular end-points (RR 1.15, 95% CI 0.98-1.33) and progression to ESRD (RR 1.08, 95% CI 0.97-1.20)). The authors also reviewed the trials for QoL outcomes and noted that this evidence was of low quality overall, and at high risk for bias due to selective reporting of outcomes.

The FDA modified dosing recommendations for ESAs again in June 2011, cautioning against raising Hb above 11 g/dL based on the risks noted in TREAT and earlier trials. (44) The new labels advised to “individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.” Later that year, the United States Center for Medicare Services, the largest payor for dialysis services in the country, changed payment rules by removing a Quality Incentive Program penalty for hemoglobin <10 g/dL, while maintaining the penalty for Hb >12 g/dL. (45)

Clinicians in the United States responded to these changing guidelines and payment incentives. ESA doses decreased in the US by approximately 30% between mid-year 2011 and 2013 in a sample of dialysis units. Average Hb levels decreased from approximately 11.2 g/dL to 10.6 g/dL in the same period. (45)

Recent Guidelines

Kidney Disease Outcomes Quality Initiative (KDIGO) published guidelines for anemia in 2012. In these guidelines, it was recommended that ESA be administered to keep the Hb greater than 9 g/dL and not to exceed 11.5 g/dL in most patients. Individualization to higher Hb levels based on subjective quality of life was permitted, though an absolute ceiling of 13 g/dL was emphasized. (33)

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) regularly updates guidelines for management of conditions including anemia of chronic kidney disease. The target Hb range has been 10-12 g/dL since 2011. Prior to that, no upper limit for Hb was recommended. In the most recent update in 2015, a footnote was added to emphasize the concern that treating to Hb levels more than 12 g/dL was associated with increased risk of mortality and cardiovascular morbidity in patients with CKD. (46) Trends in Hb targets as recommended by various agencies and organizations and changes over time are summarized in Figure 1.

Given the importance of patient-centered care in modern practice, some patients may express preferences that do not necessarily conform to the recommendations based on the best available evidence. Some authors have attempted to quantify the potential strength of patient desire to decrease transfusions or potentially improve fatigue vs. considerations such as risk of heart attack or stroke. Hauber et al. surveyed 200 patients coming to the National Kidney Foundation website for patient information. (47) They found patients would be willing to pay approximately \$94 per month to decrease anemia symptoms by 25% to by 75%. The same patients would pay \$118 to decrease blood transfusion from 2 per month to 0 (including travel and time spent in hospital getting infusion). However, they would also pay \$119 per month to decrease the risk of dying from a heart attack or stroke from 6% to 0%. While these are important questions for certain patients, the validity and generalizability of these findings is uncertain.

HIF-Stabilizers

The risk vs. benefit proposition of higher target Hb levels has been based on ESA therapy, which is associated with high blood levels of the drug and may have off-target effects detrimental to cardiovascular tissues. Hypoxia inducible factor (HIF) stabilizers, a new class of drugs to treat anemia in patients with CKD and ESRD, induce a low continuous level of endogenous erythropoietin (EPO) production in the kidney and liver and, by also inhibiting hepcidin and improving iron mobilization, are effective in raising Hb levels comparable to those achieved by ESAs.(48) Whether HIF stabilizers are associated with fewer major adverse cardiovascular events (MACE) than ESAs at comparable target Hb levels has yet to be demonstrated and phase

3 trials of HIF stabilizers are currently underway with target Hb levels in the 10-12 g/dL range. It is possible that off-target effects of the HIF stabilizers may occur since these agents also induce the production of non-EPO proteins. Should HIF stabilizers demonstrate less risk than ESAs at comparable target Hb levels, it is likely that studies will be performed to assess the MACE risk vs. QoL benefit ratio at higher target Hb levels. A favorable result would reopen the discussion of the optimal Hb level in ESRD.

Conclusion

Through the past 3 decades we have witnessed an evolution in thinking about ESAs. Initially in 1989 they were lauded as a panacea for renal anemia. The unexpected negative results of trials treating to normal Hb levels led to their classification as dangerous drugs with a progressively restrictive black box warning culminating in 2011. The first iterations of the FDA label acknowledged a QoL benefit from ESAs because they were based on early studies in patients whose Hb levels increased from the 7-8 g/dL range without treatment to the 10-11 g/dL range with treatment. Those were not placebo-controlled studies (as denying treatment to patients in the placebo arm was thought to be unethical) and QoL claims have subsequently been disallowed by the FDA if they are not based on active vs inactive treatment comparisons. All the later RCTs compared ESA treatment to Hb levels in the 9 to 11.3 g/dL range to Hb levels in the 13-14 g/dL range. Even TREAT had an ESA rescue for Hb levels less than 9 g/dL because it was thought to be unethical to allow Hb levels to go that low. The QoL benefit of higher vs lower Hb targets was less demonstrable than treatment vs no treatment, so the FDA eliminated the QoL claims for ESAs and now acknowledges only a transfusion reduction benefit. Similarly,

the FDA has taken the results of RCTs comparing target Hb levels of 9-11.3 vs 13-14 g/dL, and extrapolated the safety signal to increase at all target Hb levels and all ESA doses. It should be noted that by not providing a target Hb level for ESA dosing (just the lowest dose to avoid transfusions), the FDA is alone among evidence-based practice guidelines on the subject including KDIGO, the European Renal Association (ERA) commentary on KDIGO and NICE, all of which recommend target Hb of 9-10 to 11.5-12 g/dL. (23, 46, 49) Only the KDOQI commentary on the KDIGO guideline recommends a lower Hb target of 10-11 g/dL to be consistent with the FDA ESA label for dialysis patients. (50) However, the FDA ESA label for non-dialysis CKD patients recommends initiating ESA therapy when the Hb level is <10 then interrupting or discontinuing treatment when the Hb level is >10. (51) That is neither realistic or consistent with any other guideline on anemia treatment in patients with CKD. Medicare payment policy is based on this FDA label, making it very difficult to provide ongoing ESA therapy for Medicare patients with non-dialysis CKD.

These challenges aside, the available studies point to a target Hb of 10-11 or 10-12 g/dL as being the best compromise between efficacy and safety; KDIGO offers a target Hb of 9-11.5 g/dL, while still allowing individualization of treatment goals. Unless studies are done comparing a Hb target range of 10-11 vs. 11-12 g/dL, it is unlikely that further refinement in target Hb based on ESA therapy will be achievable in the near future. However, future investigations of HIF stabilizers could provide new answers to this persistent conundrum.

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Table 1: Major Randomized Controlled Trials of ESAs Targeting Higher and Lower Hemoglobin Levels

Study, Year	Besarab et al.	Furuland et al.	Parfrey et al.	Rossert et al.	Drüeke et al.	Singh et al.	Pfeffer et al.
	1998	2003	2005	2006	2006	2006	2009
Population/ inclusion criteria	1233 HD ¹ patients with heart failure or Ischemic Heart Disease	416 CKD (HD, PD ² & predialysis [creatinine >300 mmol/L]) patients	596 incident HD patients without symptomatic cardiac disease	390 predialysis patients (eGFR ³ 25-60 ml/min) ml/min)	603 predialysis patients (eGFR 15-35 ml/min/1.73m ²) with Hgb ⁴ 11- 12.5 g/dL	1432 predialysis patients (eGFR 15-50 ml/min/1.73 m ²)	4036 diabetic predialysis patients (eGFR 20-60 ml/min/1.73m ²)
ESA	Epoetin alfa	Epoetin alfa	Epoetin alfa	Epoetin alfa	Epoetin beta	Epoetin alfa	Darbepoetin alfa
Blinding	Double blind	Open label	Double blind	Open label	Open label	Open label	Double blind
Hgb target (g/dL)	13-15 vs. 9-11	13.5-15 (women) 14.5-16 (men)	13.5-14.5	13-15	13-15	13.5	13.0
Comparator Hgb (g/dL)	9-11	9-12	9.5-11.5	11-12	10.5-11.5	11.3	>9.0
Achieved Hgb ⁵	12.6 vs. 10.3	13.6 vs. 11.4	13.3 vs. 10.9	14.2 vs. 12	13.5 vs. 11.5	13.0 vs. 11.4	12.5 vs. 10.6
Follow up time (months)	29 (mean)	12-18 (50% completed)	22 (56% completed)	11.4 (high Hgb) 12.3 (low Hgb)	36 (79% completed)	36 (median 16)	Median 29.1 months

Primary end point	Time to death or nonfatal MI ⁶	QoL ⁷ on KDQ ⁸ , serious adverse events	Left ventricular volume index	Rate of GFR ⁹ decrease	Time to first CV ¹⁰ event	Time to death, MI, CHF ¹¹ , or stroke	Time to death, MI, CHF, stroke, angina
HR or RR (95% CI) or p- value of Primary endpoint	1.3 (0.9-1.9)	1.23 (P=0.32) for SAE's ¹²	P=0.87 for difference	P=0.976 for difference	0.78 (0.53-1.14)	1.34 (1.03- 1.74)	1.05 (0.94-1.17)
Comment	Study stopped early due to safety signal	High withdrawal rate	Relatively healthy HD population	Stopped early due to 2 pts with PRCA ¹³	Lower event rate than anticipated	Stopped early due to low probability of positive result	Excess stroke in high Hgb arm
Mortality (all-cause)	1.21 (1.01-1.46)	0.84 (0.50-1.40)	0.66 (0.33-1.30)	0.17 (0.02- 1.37)	1.48 (0.87-2.52)	1.45 (0.96- 2.19)	1.05 (0.92-1.21)
Cardiovascular events	NR ¹⁴	NR	NR	1.37 (0.93- 2.02)	1.24 (0.87-1.76)	1.06 (0.96- 1.16)	1.06 (0.96-1.16)
Access thrombosis HR/RR (95% CI)	1.37 (1.17-1.61)	2.16 (0.57-8.24)	1.19 (0.83-1.72)	NR	1.31 (0.56-3.09)	NR	NR
Stroke	1.55 (0.68-3.55)	NR	NR	NR	NR	1.00 (0.45- 2.22)	1.92 (1.38-2.68)

Table 1 Footnotes: ¹Hemodialysis; ²Peritoneal dialysis; ³estimated glomerular filtration rate; ⁴Hemoglobin; ⁵higher target achieved hemoglobin vs. lower target achieved hemoglobin; ⁶myocardial infarction; ⁷quality of life; ⁸Kidney Disease Questionnaire; ⁹glomerular filtration rate; ¹⁰cardiovascular; ¹¹congestive heart failure; ¹²serious adverse events; ¹³pure red cell aplasia; ¹⁴not reported

Figure Legend:

Figure 1. Key events in history of target hemoglobin in CKD. FDA, United States Food and Drug Administration; DOQI, Dialysis Outcomes Quality Initiative; CSN, Canadian Society of Nephrology; EBPG, European Best Practices Group; CARI, Caring for Australians with Renal Impairment; UK RA, United Kingdom Renal Association; KDOQI, Kidney Disease Outcomes Quality Initiative; UK NICE, United Kingdom National Institute for Health and Care Excellence. (4,5,9,10,13,16,27,29-33,35,38,44-46)

Key Events in History of Target Hemoglobin in CKD

